

## Cardiovascular Involvement in Behçet's Disease

Hacı Akar, MD, Cüneyt Konuralp\*\*, MD, Tekin Akpolat\*, MD

Ondokuz Mayıs University School of Medicine, Departments of

\*Cardiovascular Surgery and Internal Medicine, *Samsun*,

\*\*İstanbul Siyami Ersek Thoracic and Cardiovascular Surgery Center, Department of Cardiovascular Surgery, *İstanbul*

### Introduction

Behçet's disease (BD) is a complex, multisystemic, recurrent, inflammatory disorder (1-4). Since the first description (a triad of recurrent ulcers of the oral and genital mucosa with relapsed uveitis) by Dr. Hulusi Behçet, lots of additional organ involvements have been reported (2-12). Because of widespread manifestations of BD, physicians from many subspecialties, such as cardiologists and cardiovascular surgeons, may be involved in the care of the patients. This is especially important for the treatment of life-threatening cardiovascular complications. For this reason, cardiologists and cardiovascular surgeons need to consider BD in the differential diagnosis of many conditions and to be aware of the general principles underlying the cause of affected patients.

The etiology of BD is not known. Although viruses, streptococcal infection, autoimmune mechanisms, and endothelial cell dysfunction have been postulated in the etiopathogenesis, no definite cause has been identified so far (2-3). Clinicopathologically, BD is characterized by neutrophil and platelet hyperfunction. The disease has a chronic course with periodic exacerbations and progressive deterioration. Previous reports have shown three major pathophysiologic changes in BD (3): excessive functions of neutrophils, vasculitis with endothelial injuries, and autoimmune responses.

The diagnosis of BD relies on identification of several of its typical features. Six different criteria sets have been defined for the diagnosis of BD (3). Recently, a new set of diagnostic criteria, so called the International Study Group (ISG) Criteria, has been proposed (13).

### Cardiovascular Involvement

**Heart:** Heart lesions include coronary arteritis, coronary artery aneurysm, granulomatous endocarditis, recurrent ventricular arrhythmias, myocarditis, valvular

regurgitation, mitral valve prolapse, pericarditis, endomyocardial fibrosis, acute myocardial infarction, silent myocardial ischemia, intracardiac thrombus, left ventricular aneurysm, heart failure, aorto-atrial fistula, and amyloidosis (3, 9, 14-25). Pseudoaneurysms of the aortic arch as well as the subclavian and coronary arteries also have been described in BD (26). Cardiac thromboses are unusual in the course of BD and are frequently associated with endomyocardial fibrosis of the right heart (27). Pathogenesis of thromboses occurring in the course of BD is still unclear.

The frequency of cardiac manifestations is usually less than 2%, but was found in 17% of cases in the Japanese autopsy registry (24). According to this study, cardiomegaly was the most common cardiac alteration, followed by endocarditis, pericardial effusion, myocardial fibrosis and aortic valve disease.

The collected data from the literature regarding cardiac involvement in BD are summarized in Table-1.

**Vascular system:** Vascular involvement is the leading cause of death in BD with an approximate prevalence of 25% (9), and is seen more frequently in male than in female (36% vs. 14%) (24).

The vasculitis may involve large, medium, and small vessels of both the arterial and venous circulation. There is a tendency to thrombus formation with thrombi in the lumen of vessels showing features of inflammation and focal areas of lymphocytes.

Three forms of vascular disease are found in BD: venous occlusions, arterial aneurysms and/or arterial occlusions. Venous lesions occur more frequently than arterial lesions (88% vs. 12%) (24). Superficial thrombophlebitis is the most frequent disorder. Symptoms of vascular disease vary depending on the sites of involvement (2, 3, 9). Disorders with higher morbidity like deep venous thrombosis (DVT), and arterial aneurysms can appear, even in the lungs. Aneurysm and/or occlusion of the large arteries of the

upper (axillar artery) or lower extremities (femoral artery) are the most common types of arterial lesions. Popliteal artery aneurysm also may be seen (39).

Subcutaneous thrombophlebitis is the most frequent (47%) type of involvement of veins (9). The following most common venous lesions are superior and inferior vena cava occlusions. Chronic obliteration of large veins leads to enlargement and snake-like tortuosity of veins of the collateral circulation on the thoracic and abdominal walls. Budd-Chiari syndrome is a relatively common complication of BD (40).

Pulmonary vasculitis in Behçet's syndrome is a unique clinical and pathologic picture, differing from other vasculitides affecting the lung, presents a major threat to the patient's life.

Pulmonary artery (PA) aneurysms, pulmonary arterial and venous thrombosis and pulmonary infarction are the main features of pulmonary vascular involvement in BD. Aneurysms are more common than

thrombosis (41). Pulmonary arteries are the second most common site of arterial involvement, preceded by the aorta. Aneurysms associated with BD have a sudden onset in many cases and often result in rupture (27). Pathologically, the PA aneurysms have perivascular infiltrates around the vasa vasorum, marked intimal thickening with degenerative changes in the elastic lamina, thrombotic occlusion, and recanalization as well as fresh thrombi.

Pulmonary artery aneurysm has a very poor prognosis and is one of the leading causes of death in BD. Thirty percent of the patients with this condition die within 2 years (41). It affects mainly young men. Varying degrees of hemoptysis is the most common and predominant symptom. Rupture of an aneurysm with erosion into a bronchus and the development of in situ thrombosis from active vasculitis have been suggested as explanations for the hemoptysis. Sudden hilar enlargement or the appearance of polylobular and ro-

**Table 1. Cumulative analysis of studies evaluating cardiac involvement in Behçet's disease.**

| Author         | No of patients | Comment on study                                                                                                                            |
|----------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Kaklamani (3)  | 64             | Cardiac involvement is 2 %                                                                                                                  |
| Shahram (28)   | 3153           | Cardiac involvement is < 1 %                                                                                                                |
| Gürler (29)    | 2147           | Cardiac involvement is < 1 %                                                                                                                |
| Kone-Paul (30) | 86             | Cardiac involvement in 2 children                                                                                                           |
| Lakhanpal (24) | 170            | Autopsy of the patients showed cardiac abnormalities in 28 (17 %) patients                                                                  |
| Aksoyek (31)   | 71             | Patients with BD may have asymptomatic autonomic nervous system dysfunction                                                                 |
| Aytemir (32)   | 73             | Greater QT dispersion in BD, increased dispersion of repolarisation may account for the development of ventricular arrhythmias              |
| Göldeli (33)   | 38             | Striking increase in QT and JT dispersion in BD and this finding suggest a possible explanation for the presence of ventricular arrhythmias |
| Huong (17)     | 350            | 4 patients with endomyocardial fibrosis, BD should be added to the list of causes of endomyocardial fibrosis                                |
| Giardano (34)  | 15             | 15 patients with cardiac involvement                                                                                                        |
| Güllü (25)     | 36             | Silent myocardial ischemia is significantly higher in BD compared to the control group                                                      |
| Çalgüneri (35) | 24             | Doppler echocardiography and radionuclide ventriculography demonstrated an impairment of diastolic function                                 |
| Özkan (36)     | 65             | No significant differences in the prevalence of cardiac findings among patients with BD and controls                                        |
| Bletry (37)    | 196            | 15 cardiac manifestations observed in 12 patients                                                                                           |
| Morelli (38)   | 30             | Mitral valve prolapse and proximal aorta dilatation were observed in 50% and in 30% of the patients respectively                            |

und opacities on the chest radiograph can represent PA aneurysms. Although DVT of the lower extremities frequently accompanies PA aneurysms, pulmonary thromboembolism is very rare in BD, because the thrombi in inflamed veins are strongly adherent (42).

Patients receiving immunosuppressive treatment may show complete disappearance or regression of PA aneurysms during treatment (41). Disappearance and regression of the aneurysms are generally preceded by thrombus formation.

**Clinical diagnosis:** PA vasculitis presenting with dyspnea, cough, chest pain, and hemoptysis is not rare. In fact, hemoptysis in BD frequently leads to the misdiagnosis of pulmonary thromboembolism due to the frequent presence of a peripheral DVT and an abnormal ventilation-perfusion scan. Anticoagulation carries significant risks for patients with PA aneurysms and must be used cautiously and only after systemic immunosuppressive treatment has been started.

Aneurysms of renal arteries may be responsible for hypertension. Occlusion of the subclavian artery frequently leads to a diminished pulse in the ipsilateral upper extremity. Femoral pain, intermittent claudication, and avascular necrosis of the head of femur may occur due to either aneurysm or occlusion of the femoral artery. Involvement of the common carotid artery may result in development of hemiplegia. Ruptures of large arterial aneurysms may lead to death.

Vasculo-Behçet's disease is a type of BD with clinical features based on vasculitis of the arteries or deep veins, and is frequently life threatening (27). Early diagnosis and treatment are essential for the management of vasculo-Behçet's disease. Recent advances in the diagnosis of vasculo-Behçet's disease have been brought about by the use of radionuclide venography for DVT and CT for arterial lesions. In the treatment of vasculo-Behçet's disease, anticoagulants and fibrinolytic agents are beneficial in controlling DVT. Operative therapy is often recommended for the management of arterial aneurysm, because rupture of arterial aneurysm is the leading cause of death in patients with BD.

**Imaging techniques:** Echocardiography is useful in documenting the presence of thrombus and valvular lesions. Angiography and CT are methods commonly used to evaluate cardiovascular involvement, but they carry risk for complications. Venous puncture, intravenous infusion, rapid injection of a large bolus of contrast media, and insertion of a venous catheter may initiate venous thrombosis in BD (43, 44). Venipuncture

for any reason, even in the absence of a contrast agent injection, may increase the risk for venous thrombosis. An increased incidence of aneurysm formation at the puncture site has been reported after venography and arterial puncture (9, 45-47). Therefore, it is desirable to avoid intravenous injections, arteriography, and venography in these patients. Doppler ultrasonography, MRI and MR angiography are safe and noninvasive methods that can be used to confirm and monitor cardiovascular involvement in BD. Helical CT is currently the method of choice for the diagnosis of pulmonary vascular lesions, because it provides excellent vascular images with only a small quantity of contrast material. Pulmonary artery aneurysms are located most frequently in the right lower lobar arteries, followed by the right and left main PA (48).

Digital subtraction angiography has also been used in the diagnosis but it may be inadequate if aneurysms or vessels are completely thrombosed.

**Prognosis:** The prognosis is good unless vital organs are affected. Patients with vascular (Budd-Chiari syndrome, PA aneurysm), central nervous system involvement and amyloidosis carry poor prognosis (10-12, 40). The prognosis of aneurysms is worse than that of occlusive lesions (3).

**Treatment:** Current treatment is tailored according to the site and severity of BD. Because BD usually runs an undulating course of exacerbations and remissions, it is generally difficult to evaluate the efficacy of therapy. Treatment of BD is symptomatic and empirical and varies according to the clinical manifestations. The mainstay of treatment in BD is immunosuppressive therapy as in other severe vasculitis. Other treatment modalities should be used only in combination with this therapy and as palliative measures for specific complications. Although definitive data do not exist, there is a tendency among physicians to prescribe colchicine to all patients (44). Topical preparations of local anesthetic and local steroid preparations provide symptomatic relief and probably shorten the duration of oral ulcers. Thalidomide, simple analgesics, anti-inflammatory agents, interferon- $\alpha$ , prophylactic benzathine penicillin, azathioprine and cyclosporine are treatment options for other manifestations of BD (3, 49, 50). A controlled, long-term study regarding the treatment of vascular BD has not yet been reported. Antiplatelet agents such as low-dose aspirin and dipyridamole are recommended for venous involvement, but a controversy exists on this subject (9, 49). Routine anticoagulation with heparin or oral antico-

agulants is not advised. As in PA aneurysm, combination of cyclophosphamide and methylprednisolone is most frequently used for patients with severe vasculitis. Pulmonary artery aneurysms in BD may become smaller or disappear with medical treatment. Mural thrombotic changes may be observed during the regression of PA aneurysms (48).

**Surgical therapy:** Cardiothoracic problems (PA aneurysm, valvular lesions, coronary artery or ventricular aneurysms) may require surgical intervention. But, surgical therapy of BD always challenges cardiovascular surgeons with a high frequency of complications. The risk of postoperative regurgitation and postoperative valve detachment is high in these patients (51, 52). Aneurysms limited to the extremities could be ligated without disabling ischemia. Tube graft insertion is suggested for abdominal aortic aneurysms (53). Surgery, when feasible, is indicated for aneurysms because they entail a high risk of rupture. The main problem facing the vascular surgeon is the 25%-incidence of recurrent anastomotic aneurysms after both inlay graft repair and patching. Appropriate operative procedures, including an adequate choice of anastomotic sites and reinforcement of the suture, may reduce the incidence of complications in patients with arterial aneurysms. Postoperative corticosteroids and/or immunosuppressives are necessary to prevent arterial relapse (54). After bypass for lower limb arterial lesions, anticoagulation is warranted to prevent graft thrombosis (26).

If endomyocardial fibrosis is complicated by cardiac failure, surgical excision may be useful in the short term (3).

### Summary and Conclusions

Behçet's disease is a vasculitis disorder in which the etiopathogenetic pathway has not been clarified yet. Many organs and systems including the heart may be affected in BD. We affirm that pathological heart features are not so uncommon as previously reported in the literature and constant evaluation for the cardiovascular system in asymptomatic patients is needed. Therefore; management of BD may involve rheumatologists, gastroenterologists, neurologists, immunologists and cardiologists. Close liaison among these clinicians may be necessary to provide optimum care for the patient with BD. It is expected that clarification of the etiopathogenesis of BD will lead us to the better treatment options.

### References

- Behçet H. Über rezidivierende Aphthose, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. *Dermatol Wochenschr* 1937; 105:1152-7.
- Shimizu T, Ehrlich GE, Inaba G, Hayashi K. Behçet's disease (Behçet's syndrome). *Semin Arthritis Rheum* 1979; 8: 223-60.
- Kaklamani VG, Vaiopoulos G, Kaklamani PG. Behçet's disease. *Semin Arthritis Rheum* 1998; 27: 197-217.
- Akpolat T. Management of patient with Behçet's disease. *Nephrol Dial Transplant* 1998; 13: 3000-2.
- Akpolat T, Koç Y, Yeniay İ, et al. Familial Behçet's disease. *Eur J Med* 1992; 1: 391-5.
- Akpolat I, Akpolat T, Danacı M, Baris YS, Kaya N, Kandemir B. Behçet's disease and amyloidosis: Review of the literature. *Scand J Rheumatol* 1997; 26: 477-9.
- Yazıcı H, Yurdakul S, Hamuryudan V. Behçet's syndrome. *Curr Opin Rheumatol* 1999; 11: 53-7.
- Sakane T, Takeno M, Suzuki N, et al. Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
- Koç Y, Güllü İ, Akpek G, et al. Vascular involvement in Behçet's disease. *J Rheumatol* 1992; 19: 402-10.
- Yazıcı H, Başaran G, Hamuryudan V, et al. The ten-year mortality in Behçet's syndrome. *Br J Rheumatol* 1996; 35: 139-41.
- Wolf SM, Schotland DL, Phillips LL. Involvement of nervous system in Behçet's syndrome. *Arch Neurol* 1965; 12: 315-25.
- Akpolat T, Akpolat İ, Kandemir B. Behçet's disease and AA type amyloidosis. *Am J Nephrol* 2000; 20: 68-70.
- International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
- Huycke EC, Robinowitz M, Cohen IS, et al. Granulomatous endocarditis with systemic embolism in Behçet's disease. *Ann Intern Med* 1985; 102: 791-3.
- Schiff S, Moffatt R, Mandel WJ, Rubin SA. Acute myocardial infarction and recurrent ventricular arrhythmias in Behçet's syndrome. *Am Heart J* 1982; 103: 438-40.
- Hamuryudan V, Yurdakul S, Kural AR, Ince U, Yazıcı H. Diffuse proliferative glomerulonephritis in Behçet's syndrome. *Br J Rheumatol* 1991; 30: 63-4.
- Huong DL, Wechsler B, Papo T, et al. Endomyocardial fibrosis in Behçet's disease. *Ann Rheum Dis* 1997; 56: 205-8.
- Ioakimidis D, Georganas C, Panagoulis C, et al. A case of Adamantiadis-Behçet's syndrome presenting as myocardial infarction. *Clin Exp Rheumatol* 1993; 11: 183-6.
- Nakata Y, Awazu M, Kojima Y, Tokumura M, Yamagishi H, Yamashita N. Behçet's disease presenting with a right atrial vegetation. *Pediatr Cardiol* 1995; 16: 150-2.
- Vanhaleweyck G, el-Ramahi KM, Hazmi M, Sieck JO, Zaman L, Fawzy M. Right atrial, right ventricular and left ventricular thrombi in (incomplete) Behçet's disease. *Eur Heart J* 1990; 11: 957-9.
- Rolland JM, Bical O, Laradi A, et al. False aneurysm of the left ventricle and coronary aneurysms in Behçet's disease. *Arch Mal Coeur Vaiss* 1993; 86: 1383-5.

22. Melua A, Campbell N, McCluskey D, MacGowan SW. Aorto-atrial fistula without aneurysm formation in Behcet's disease. *Heart* 1998; 80: 200-1.
23. Beroniade V. Amyloidosis and Behcet's disease. *Ann Intern Med* 1975; 83: 904-5.
24. Lakhanpal S, Tani K, Lie JT, Katoh K, Ishigatsubo Y, Ohokubo T. Pathologic features of Behcet's syndrome: a review of Japanese autopsy registry data. *Hum Pathol* 1985; 16: 790-5.
25. Güllü İH, Benekli M, Müderrisoğlu H, et al. Silent myocardial ischemia in Behcet's disease. *J Rheumatol* 1996; 23: 323-7.
26. Le Thi Huong D, Wechsler B, Papo T, et al. Arterial lesions in Behcet's disease. A study in 25 patients. *J Rheumatol* 1995; 22:2103-13.
27. Sasaki Sh, Yasuda K, Takigami K, Shiiya N, Matsui Y, Sakuma M. Surgical experiences with peripheral arterial aneurysms due to vasculo-Behcet's disease. *J Cardiovasc Surg (Torino)* 1998; 39:147-50.
28. Shahram F, Davatchi F, Akbarian M, et al. The 1996 survey of Behçet's disease in Iran, study of 3153 cases. *Revue du Rhumatisme* 1996; 63: 538.
29. Gürler A, Boyvat A, Tursen U. Clinical manifestations of Behcet's disease: an analysis of 2147 patients. *Yonsei Med J* 1997; 38: 423-7.
30. Kone-Paut I, Yurdakul S, Bahabri SA, et al. Clinical features of Behcet's disease in children: an international collaborative study of 86 cases. *J Pediatr* 1998; 132: 721-5.
31. Aksoyek S, Aytemir K, Özer N, Ozcebe O, Oto A. Assessment of autonomic nervous system function in patients with Behcet's disease by spectral analysis of heart rate variability. *J Auton Nerv Syst* 1999; 77: 190-4.
32. Aytemir K, Özer N, Aksoyek S, Ozcebe O, Kabakci G, Oto A. Increased QT dispersion in the absence of QT prolongation in patients with Behcet's disease and ventricular arrhythmias. *Int J Cardiol* 1998; 67: 171-5.
33. Göldeli O, Ural D, Komşuoğlu B, Ağaçdiken A, Dursun E, Çetinarslan B. Abnormal QT dispersion in Behcet's disease. *Int J Cardiol* 1997; 61: 55-9.
34. Giordano N, Senesi M, Mondillo S, et al. Heart involvement in Behcet's disease: a personal caseload en review of the literature. *G Ital Cardiol* 1996; 26: 519-25.
35. Çalgüneri M, Erbaş B, Kes S, Karaaslan Y. Alterations in left ventricular function in patients with Behcet's disease using radionuclide ventriculography and Doppler echocardiography. *Cardiology* 1993; 82: 309-16.
36. Özkan M, Emel O, Özdemir M, et al. M-mode, 2-D and Doppler echocardiographic study in 65 patients with Behcet's syndrome. *Eur Heart J* 1992; 13: 638-41.
37. Bletry O, Mohattane A, Wechsler B, et al. Cardiac involvement in Behcet's disease. 12 cases. *Presse Med* 1988; 17: 2388-91
38. Morelli S, Perrone C, Ferrante L, et al. Cardiac involvement in Behcet's disease. *Cardiology* 1997; 88: 513-7.
39. Akar, H, Akpolat, T, Kolbakir, F, Konuralp, C, Akpolat, İ, Danacı, M. Behçet's disease and popliteal artery aneurysm: a case report and review of the literature. *Eur J Vasc Endovasc Surg Extra* 2001; 2: 25-8.
40. Bayraktar Y, Balkancı F, Bayraktar M, Calguneri M. Budd-Chiari syndrome: a common complication of Behçet's disease. *Am J Gastroenterol* 1997; 92: 858-62.
41. Erkan F, Gül A, Tasalı E. Pulmonary manifestations of Behçet's disease. *Thorax* 2001; 56:572-8.
42. Bradbury AW, Milne AA, Murie JA. Surgical aspects of Behcet's disease. *Br J Surg* 1994; 81:1712-21.
43. Berkmen T. MR angiography of aneurysms in Behcet disease: a report of four cases. *J Comput Assist Tomogr* 1998; 22: 202-6.
44. Tunacı A, Berkmen YM, Gökmen E. Thoracic involvement in Behcet's disease: pathologic, clinical, and imaging features. *Am J Roentgenol* 1995; 164: 51-6.
45. Malik KJ, Weber SL, Sohail S, Balaan MR. Hilar mass and papilledema on presentation. *Chest* 1998; 113: 227-9.
46. Hamza M. Large artery involvement in Behcet's disease. *J Rheumatol* 1987; 14: 554-9.
47. Kingston M, Ratcliffe JR, Alltree M, Merendino KA. Aneurysm after arterial puncture in Behcet's disease. *Br Med J* 1979; 1: 1766-7.
48. Tunacı M, Ozkorkmaz B, Tunacı A, Gul A, Engin G, Acunas B. CT findings of pulmonary artery aneurysms during treatment for Behcet's disease. *Am J Roentgenol* 1999; 172:729-33.
49. Yazıcı H, Barnes CG. Practical treatment recommendations for pharmacotherapy of Behçet's syndrome. *Drugs* 1991; 42: 796-804.
50. Çalgüneri M, Ertenli İ, Kiraz S, Erman M, Celik I. Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996; 192: 125-8.
51. Tanimoto K, Ishizuka N, Ram SB, et al. Treatment of cardiovascular Behcet's disease: a problem with valve replacement. *J Cardiol* 1998; 31 (Suppl 1): 75-82.
52. Ando M, Kosakai Y, Okita Y, Matsukawa R, Takamoto S. Surgical treatment for aortic regurgitation caused by non-specific aortitis. *Cardiovasc Surg* 1999; 7: 409-13.
53. Tüzün H, Besirli K, Sayın A, et al. Management of aneurysms in Behcet's syndrome: an analysis of 24 patients. *Surgery* 1997; 121: 150-6.
54. Mahendran C, Singh P, Mani NB, Jindal SK. Successful treatment of pulmonary artery aneurysms secondary to possible Behcet's disease. *Respiration* 2002; 69:355-8.

## DÜZELTME

Anadolu Kardiyoloji Dergisinin Haziran 2003 sayısının Eğitim kısmında yayınlanan "Fibrinolitik İlaçların Kullanımı" isimli yazının, 165. sayfa 2. sütun yukarıdan 19 satır: "streptokinaz veya anistreplaz verilen hastalar..." yerine "streptokinaz veya rt-PA verilen hastalar için..." olması gerekir. Düzeltir, özür dileriz.